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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/508,339	TESHIMA ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20 Sepetmber 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending in the current application.

2. This application is a national stage of PCT/JP03/03925 filed March 28, 2003. and claims priority to Japanese Application 200293398 filed March 29, 2002.

Claim Rejections - 35 USC § 101/112

3. Claim 18-20 provides for the use of "ORL-1 receptor agonists", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

4. Claims 18-20 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). See MPEP 2173.05(q) for a discussion of "use" claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 15-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(A) The breadth of the claims: The claims are very broad encompassing a variety of compounds bearing multiple substitutions for treating a various sleep disorders. **(B) The nature of the invention:** This is a medicinal invention requiring the synthesis of compounds and use of the compounds. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing physician or pharmacist. **(C) The state of the prior art:** Little prior art exists on these complex compounds, however the synthesis will be evaluated on what is known using scientific principles. **(E) The level of predictability in the art:** Medicine and in particular treating sleep disorders is unpredictable (*see below*) **(F) The amount of direction provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** ORL-1 antagonists may no doubt have a utility, however the use of these compounds in treatment has not been shown. The "how to use" requirement of 35 U.S.C. 112 are not met by disclosing a pharmacological activity of the claimed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation (In

re Diedrich (CCPA 1963) 318 F2d 946, 138 USPQ 128; In re Gardner et. al. (CCPA 1970) 427 F2d 786, 166 USPQ 138). One reviewer put it this way:

> "Although one may successfully identify substances that effect circadian rhythmicity when the biochemical milieu of the clock is successfully manipulated, one is immediately faced with several problems in generalizing from those changes to the clinical situation. First, most of the peptides and neurotransmitters listed in Table 1 are not unique to the SCN and are often relatively ubiquitous in their CNS distribution. They are involved in the regulation of a number of more complex behaviours, as well as physiological and endocrinological processes. Therefore, by some means, a chronobiotic would have to stimulate the SCN selectively, leaving the same transmitter and peptide systems in the rest of the brain stimulated. Second, when light induces phase-shifts, several transmitter systems may act synergistically, and this synergistic interaction could be quite complex. Therefore, administration of a drug affecting a single transmitter system may have little effect on SCN output. Third, ideally the chronobiotic would have to be administered orally, for convenience, but survive gastric digestion. At the same time, the peripheral nervous system and visceral organs would have to remain unaffected. Finally, many compounds may affect complex behavioural systems, such as thought, cognition, and motivational states. Inferring a chronobiotic effect for a drug on the basis of an action on complex cognitive or behavioural systems will always be problematic unless nondrug interventions that produce similar behavioural changes are also considered chronobiotic. While it is apparent that powerful chronobiotics are now on the threshold of discovery, a great deal of work has to be conducted on aspects of dose and timing. The possibility of tolerance developing with prolonged use is pertinent to choice of doses. Despite these barriers, as the applied application and commercial advantages of any chronobiotic is large, there

> undoubtedly will be an intensification of research for other compounds in the foreseeable future." Drew Dawson and Stuart Maxwell Amstrong "Chronobiotics-Drugs That Shift Rhythms" *Pharmacology and Therapeutics* **1996**, *69*, 15-36.

The endogenous ligand for ORL-1, N/OFQ an agonist, is known to have many functions related to anxiety, pain and other physiological processes. It seems very unlikely that a medical doctor or Pharm. D. would know what to do with these compounds. Indeed one reviewer remarked: "When treating sleep disorders of the circadian kind, special care must be given to distinguish compounds with chronobiotic properties from those with hypnotic effects. Whereas a chronobiotic may induce sleep by shifting the sleep–wake cycle so that sleep onset occurs earlier, a hypnotic will simply induce sleep without affecting the circadian mechanism." Yvan Touitou, André Bogdan "Promoting adjustment of the sleep–wake cycle by chronobiotics" *Physiology & Behavior* **2007**, *90*, 294–300. These compounds are active at the opioid like receptor which may mean that they are causing a simple sedative or hypnotic effect. The factors outlined in *In Re Wands* mentioned above apply here. It is very clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation for the plethora of sleep disorders mentioned.

6. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matterwhich was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The MPEP states that the purpose of the written description requirement is to ensure

that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other

than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what does not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is

sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a function with no structure i.e. any agonist.

(1) Level of skill and knowledge in the art:

In order for a molecule to be used it must exist. *Vide Supra (at 4).*

(2) Partial structure:

Claims 10-14 have structures, but the claims rejected here have none.

(3) Physical and/or chemical properties and (4) Functional characteristics:

Vide Supra (at 4).

(5) Method of making the claimed invention:

No method is given to make the invention. *Vide Supra (at 5).* As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1-9 is/are generic, with respect to all possible compounds or even perhaps non-compounds encompassed by the claims. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification has no species to reflect this variance in the genus. While having written description of other compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

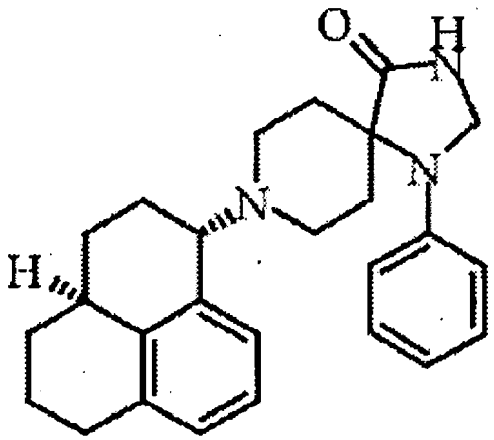
7. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over unpatentable over Francois Jenck, Juergen Wichmann, Frank M. Dautzenberg, Jean-Luc Moreau, Abdel M. Ouagazzal, James R. Martin, Kenneth Lundstrom, Andrea M. Cesura, Sonia M. Poli, Stephan Roever, Sabine Kolczewski, Geo Adam, and Gavin Kilpatrick "A synthetic agonist at the orphanin FQ/nociceptin receptor ORL1: Anxiolytic profile in the rat" *Proceedings of the National Academy of Sciences* **2000**, *97*, 4938-4943 and Ito, F. et. al. 1999 WO 9936421 A1 and Tulshian, D. et. al. WO 2000006545. The factual inquiries set forth in *Graham* **v.** *John Deere*

Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

Determination of the scope and content of the prior art

(MPEP 2141.01)

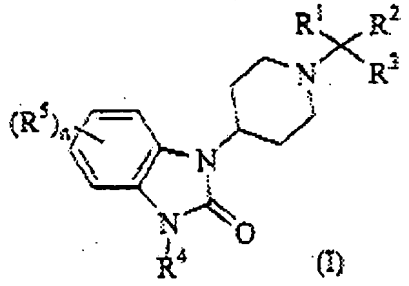
Jenck et. al. teaches several compounds that are ORL-1 agonists and very similar to the ones of the instant case. The most potent compound that showed excellent selectivity over other opioid receptor subtypes was the compound shown below:



Ro 64-6198 (1S, 3aS-enantiomer)

Ito, F. et. al. teaches a large group of 1-piperidin-4-yl-2-benzimidazolone ORL-1 receptor agonists. The 89 compounds of Table 1 (pg. 59 are shown below)

TABLE



(I)

Example No.	R^1	R^2	R^3	R^4	R^5
1	cyclohexyl		Ph	H	H
2	cyclohexyl		benzyl	H	H
3	cyclohexyl		methyl	H	H
4	cyclohexyl		ethenyl	H	H
5	cyclohexyl		2-thienyl	H	H
6	cyclohexyl		ethynyl	H	H
7	cyclohexyl		propyl	H	H
8	cyclohexyl		4-Cl-Ph	H	H
9	cyclohexyl		4-methoxy-Ph	H	H
10	methyl	methyl	Ph	H	H
11	methyl	methyl	benzyl	H	H
12	methyl	methyl	2-thienyl	H	H
13	methyl	methyl	4-F-Ph	H	H
14	methyl	methyl	4-methyl-Ph	H	H
15	methyl	methyl	3-Ph-propyl	H	H
16	methyl	methyl	4-methoxy-Ph	H	H
17	cycloheptyl		Ph	H	H
18	cycloheptyl		2-thienyl	H	H
19	ethyl	ethyl	Ph	H	H
20	ethyl	ethyl	2-thienyl	H	H
21	cyclobutyl		Ph	H	H
22	cyclobutyl		2-thienyl	H	H
23	cyclopentyl		Ph	H	H
24	cyclohexyl		Ph	H	6-Cl
25	cycloheptyl		Ph	H	6-Cl
26	cyclopropyl		Ph	H	H
27	cycloheptyl		Ph	methyl	H
28	cycloheptyl		Ph	H	5-methoxy
29	dimethylcyclohexyl		Ph	H	H

TABLE (continued)

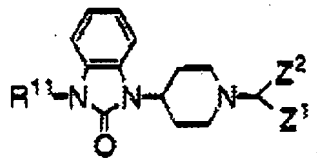
Example No.	R^1	R^2	R^3	R^4	R^5
30	cyclononyl		n-propyl	H	H
31	bicyclo[4.3.0]nonan-8-yl		Ph	H	H
32	cyclooctyl		Ph	H	H
33	cyclononyl		Ph	H	H
34	cyclodecyl		Ph	H	H
35	cycloundecyl		Ph	H	H
36	cyclododecyl		Ph	H	H
37	cycloheptyl		4-F-Ph	H	H
38	cycloheptyl		3-F-Ph	H	H
39	cycloheptyl		4-methoxy-Ph	H	H
40	cycloheptyl		3-methoxy-Ph	H	H
41	cycloheptyl		2-methoxy-Ph	H	H
42	4-t-butylcyclohexyl		Ph	H	H
43	cycloheptyl		Ph	H	4-F
44	cycloheptyl		Ph	H	5-F
45	cycloheptyl		Ph	H	6-F
46	cycloheptyl		Ph	H	5-Me
47	cycloheptyl		Ph	H	6-Me
48	cycloheptyl		Ph	H	5-CF_3
49	cycloheptyl		Ph	H	Ph-CO-
50	cycloheptyl		Ph	H	7-Cl
51	cycloheptyl		Ph	H	5,6-di-F
52	cycloheptyl		Ph	H	5,6-di-Cl
53	spiro[5.5]undecan-3-yl		propyl	H	H
54	isopropylidenecyclohexyl		propyl	H	H
55	cyclononyl		methyl	H	H
56	cyclononyl		ethyl	H	H
57	cyclooctyl		methyl	H	H
58	cyclooctyl		ethyl	H	H
59	cyclooctyl		propyl	H	H
60	cyclohept-4-enyl		Ph	H	H
61	cyclohept-4-enyl		methyl	H	H
62	cyclohept-4-enyl		ethyl	H	H
63	cyclohept-4-enyl		propyl	H	H
64	cycloheptyl		Ph	aminoethyl	H
65	cycloheptyl		Ph	guanidinoethyl	H
66	cycloheptyl		Ph	methylaminoethyl	H
67	cycloheptyl		Ph	acetylaminoethyl	H
68	cycloheptyl		Ph	L-prolinamidoethyl	H

TABLE (continued)

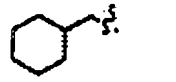
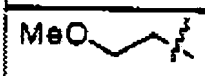
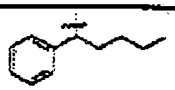
Example No.	R^1	R^2	R^3	R^4	R^5
69	cycloheptyl		Ph	pyridyl-CONH-ethyl	H
70	cycloheptyl		Ph	aminopropyl	H
71	cycloheptyl		Ph	aminohexyl	H
72	cycloheptyl		Ph	piperidinoethyl	H
73	cycloheptyl		Ph	morpholinoethyl	H
74	cycloheptyl		Ph	dimethylaminoethyl	H
75	cycloheptyl		Ph	diisopropylaminoethyl	H
76	cycloheptyl		Ph	piperidinylethyl	H
77	cycloheptyl		Ph	pyrrolylethyl	H
78	cycloheptyl		Ph	piperazinoethyl	H
79	cycloheptyl		Ph	pyridinylpropyl	H
80	cycloheptyl		Ph	amidinopiperazinoethyl	H
81	cycloheptyl		Ph	n-butyl	H
82	cycloheptyl		Ph	benzyl	H
83	cycloheptyl		Ph	NH_2-CH_2CONH-$(CH_2)_2$-	H
84	cycloheptyl		Ph	aminoacetylpiperazinoethyl	H
85	cycloheptyl		Ph	methylsulfonylaminoethyl	H
86	cycloheptyl		Ph	acetyl	H
87	cycloheptyl		Ph	pyrimidinylaminoethyl	H
88	cycloheptyl		Ph	pyrimidinylpiperazinoethyl	H
89	cyclohept-4-enyl		Ph	aminoethyl	H

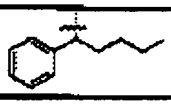
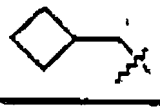
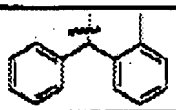
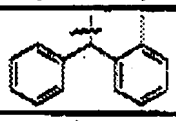
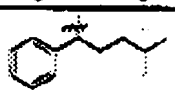
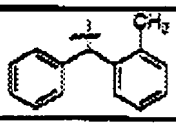
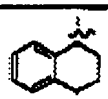
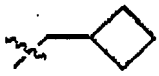
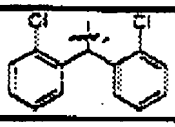
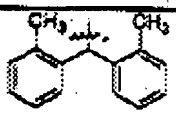
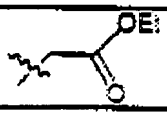
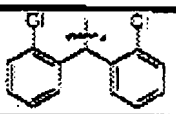
Tulshian et. al. also teaches a large group of 1-piperidin-4-yl-2-benzimidazolone ORL-1 receptor agonists. The 50 or so compounds of Table 5 (pg. 38-41 38) are shown below:

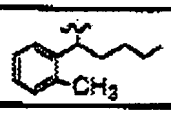
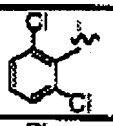
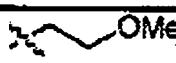
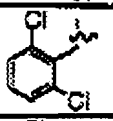
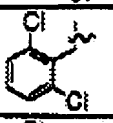
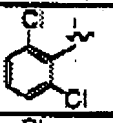
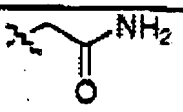
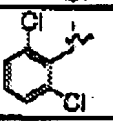
Table 5



wherein R^{11}, Z^1 and Z^2 are as defined in the following table, wherein Ac is acetyl, Me is methyl and Et is ethyl::

R^{11}	$CH(Z^1)(Z^2)$	Physical Data
H	Benzhydryl	
	Benzhydryl	$C_{32}H_{37}N_3O$:HCl CI 480 (100), 167.25 (22)
	Benzhydryl	$C_{29}H_{31}N_3O_3$:HCl CI 470.15 (100), 167.25 (25)
	Benzhydryl	$C_{29}H_{31}N_3O$:HCl CI 438.20 (100), 167.25 (29)
	Benzhydryl	$C_{30}H_{33}N_3O$:HCl FAB 452.3 (100), 167.0 (92)
	Benzhydryl	$C_{29}H_{33}N_3O$:HCl CI 440.20 (100), 167.25 (22)
Me	Benzhydryl	$C_{25}H_{27}N_3O$:HCl CI 398.15 (100), 167.25 (39)
Ethyl	Benzhydryl	$C_{27}H_{29}N_3O$:HCl CI 412.15 (100), 167.25 (32)
n propyl	Benzhydryl	C28H31N3O:HCl ESI 426.1(14), 167 (100)
n butyl	Benzhydryl	$C_{29}H_{33}N_3O$:HCl ESI 440.10 (100), 167.10 (33)
isopropyl	Benzhydryl	$C_{28}H_{31}N_3O$:HCl ESI 446.10 (28), 167. (100)
	Benzhydryl	$C_{28}H_{31}N_3O_2$:HCl ESI 442.10 (15), 167. (100)
	Benzhydryl	$C_{27}H_{29}N_3O_2$:HCl FAB 428.3 (65), 232.1 (57)
H		$C_{23}H_{29}N_3O$:HCl ESI 364.1 (58), 218.1 (100)

HO 		$C_{25}H_{33}N_3O_2$:HCl ESI 408.1 (93), 262.1 (100)
n pentyl	Benzhydryl	$C_{30}H_{35}N_3O$:Hcl ESI 454.1 (46), 167.1 (100)
n-hexyl	Benzhydryl	$C_{31}H_{37}N_3O$:HCl ESI 468.1 (26), 167 (100)
	Benzhydryl	$C_{29}H_{31}N_3O_2$:HCl ESI 442.10 (15), 167 (100)
		$C_{31}H_{35}N_3O$:HCl ESI 466.1 (44), 181.1 (100)
MeO 		$C_{29}H_{33}N_3O_2$:HCl ESI 456.1 (48), 181.10(100)
H		$C_{24}H_{31}N_3O$:HCl CI 378.25 (100), 306.20 (22), 218.20 (24)
H		$C_{28}H_{27}N_3O$:HCl ESI 398.10 (44), 181.1 (100)
		$C_{27}H_{33}N_3O$:HCl ESI 416.10(36), 286.1 (39)
		$C_{30}H_{31}N_3OCl_2$:HCl ESI 522.1 (79), 521.1 (48), 520 (100)
	Benzhydryl	$C_{30}H_{34}N_2O$:HCl CI 439.25 (100), 168.30 (20)
H		$C_{27}H_{29}N_3O$:HCl CI 412.20(32), 218.20 (42), 195.35 (100)
	Benzhydryl	$C_{29}H_{31}N_3O_3$:HCl ESI 470.1 (100), 167.1 (77.40)
H		$C_{25}H_{23}N_3Cl_2O$:HCl ESI 452.1 (100), 235 (85)

H		$C_{24}H_{31}N_3O$ FAB 378.4 (100), 218.2 (30)
	Benzhydryl	$C_{31}H_{35}N_3O_3$ 498.2 (100), 167.1 (90)
	Benzhydryl	$C_{28}H_{31}N_3O_3$ ESI 470.1 (100), 167.1 (55)
		$C_{23}H_{27}Cl_2N_3O$ ESI 434.1 (80), 432.1 (100)
		$C_{22}H_{25}Cl_2N_3O_2$ ESI 436.1 (58), 434.1 (100)
		$C_{23}H_{27}Cl_2N_3O$ ESI 434.1 (35), 432.1 (100)
		$C_{24}H_{27}Cl_2N_3O$ ESI 446.1 (77)), 444.1 (100)
		$C_{21}H_{22}Cl_2N_4O_2$ FAB 435.1 (78), 433.1 (100)

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

Ito et. al. and Talushian et al. do not expressly teach acenaphthenyl for R_1-R_2 or Z1-Z2 respectively, however they teach all the other structural features of the instantly claimed compounds.

Jenck et. al. teach compounds similar to those of the instant case, that have the acenaphthenyl group on the piperidinyl Nitrogen. This exact modification is what distinguishes the compounds of Ito and Talushian from those of the instant case.

Finding of prima facie obviousness
Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the compounds Ito et. al. and Talushian et al. as suggested by Jenck et. al. to produce the instant invention. One of ordinary skill in the art would have been motivated to do this because the introduction of the acenaphthene group gave superb selectivity over other opiod receptor subtypes (more than 100 fold Jenck ibid.) and ORL-1 agonists may be valuable for the treatment of disorders. A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by compound A of the specification *Biorganic and Medicinal Chemistry Letters* **1999**, *9*, 2343. Cited by applicant as an ORL-1 agonist which meets the instant claims on the IDS and shown to be functional in the Figures of the specification see pg. 34.

Conclusions

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

R Desai 7/12/07

RITA DESAI
PRIMARY EXAMINER